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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,616	BERNARD ET AL.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003 and 09 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14,17-20,23-35,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14,17-20,23-35,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *16*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

I. The objection of claim 22 will not be maintained in light of the amendment.

II. The rejection of claim 23 under 35 USC 112, second paragraph, will not be maintained in light of the amendment.

III. The rejection of claim 40 under 35 USC 102(b) as being anticipated by Tran et al. will not be maintained in light of the amendment.

IV. The rejection of claim 13, 14, 17-20, 23-35 and 40 under 35 USC 112, first paragraph, will be maintained for the reason of the record.

V. The rejection of claims 13-14, 20, 31, 32, 33 and 40 under 35 USC 102(b) as being anticipated by Rotstein et al. will be maintained for the reason of the record.

Supplemental Office Action

1. This Office Action supercedes the previous Office Action mailed on February 03, 2004. The Supplemental Amendment filed October 09, 2003 that contains claim 41 was not considered in the Office Action on February 03, 2004. Accordingly, the examiner withdraws the finality of the Office Action mailed on February 03, 2004.

Status of Application

2. Acknowledgment is made of applicant's filing of Amendment filed September 11, 2003 and Supplemental Amendment filed October 09, 2003. By the Amendment filed September 11,

2003, claims 1-12 and 36-39 have been cancelled and claims 13, 16, 18, 20-23 and 32 have been amended. By the Amendment filed October 09, 2003, claim 41 has been newly added.

3. Claims 13-14, 17-20, 23-35 and 40-41 are currently pending for the prosecution on the merits.

Information Disclosure Statement

4. Acknowledgment is made of applicant's filing of non-patent publications in PTO form-1449 dated September 11, 2003. Applicants state that those are not cited as references but in support of the level of one of ordinary skill in the art. Accordingly, it has been placed in the application file, but the information referred to therein has not been considered as to the merits. In any case, applicants desire for the examiner to consider those references, applicants is advised to file the information disclosure statement in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13-14, 17-20, 23-35 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present claim is drawn to a method of treating or preventing a disease condition caused by exacerbated by an MPV comprising administering a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene, namely compounds of formula (I) or (II).

The instant specification discloses that the claimed disease conditions include cervical cancer, precursor lesions of this malignant neoplsia which are called cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL), genital warts and common warts and plantar warts which are commonly caused by HPV (page 1, line 25 thru page 2, line 1; page 6, lines 17-28). Furthermore, the instant specification refers to Table 1 of page 37 of Human Papillomarviruses [Volumne 65 (1995) IARC Monographs on the evolution of carcinogenic risks in Humans, The International Agency for Research on Cancer, World Health Organization, IARC, Lyon, France} as the claimed disease conditions that may be treated in accordance with the present invention (page 7, lines 5-9).

The instant invention is based on studies regarding (i) the activity of the specific compounds represented by formula (I) or (II), namely C16, which have been identified by TSQ assay and assay of measuring the ability of the compound to inhibit the binding of the E6 protein to E6AP or E6BP, in killing HPV containing cell lines as HeLa, SiHa and Caski (Examples 2-5), specifically HPV16-positive and HPV18-positive cell lines. The instant specification provides sufficient information regarding the activity of C16, having at least 30% zinc release in TSQ assay and the activity of inhibiting the binding of the E6 protein to E6AP or E6BP, in inhibiting growth of HPV16-postive and HPV18-positive cervical tumor cell lines. However, the instant specification (Tables 1-3) fails to provide adequate written description for whether all the

compounds represented by formula (I) or (II) which have been identified by TSQ assay (at least 30% zinc release) and assay of measuring the ability of the compound to inhibit the binding of the E6 protein to E6AP or E6BP would have the cytotoxic effects on HPV containing cell lines, namely HPV16-positive and HPV18-positive cell lines. In fact, for example, R25 does not show any cytotoxic effects (also, C27 and R24 do not show any specific cytotoxic effects).

The specification do not clearly provide an adequate representation regarding (i) whether all the claimed compounds represented by formula (I) or (II) that are identified by TSQ assay and assay of measuring the ability of the compound to inhibit the binding of the E6 protein to E6AP or E6BP, are effective in inhibiting the growth of HPV16-postive and HPV18-positive cervical tumor cell lines; (ii) whether the claimed compounds capable of facilitating the disruption of two Cys-X2-Cys-X29-Cys-X2-Cys zinc fingers of HPV E6 and E7 are effective in inhibiting growth of other HPV containing cell lines (other than HPV16-positive and HPV18-positive cell lines); and (iii) the conclusion of the claimed method of treating or preventing said disease in animal from in-vitro study of using C16 in inhibiting growth of HPV16-postive and HPV18-positive cervical tumor cell lines. In addition, the specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of inhibiting of growth of HPV16-postive and HPV18-positive cervical tumor cell lines (in-vitro), the skilled artisan cannot envision the claimed method of treating said disease conditions in animal nor the method of inhibiting the growth of non-HPV16-positive or non-HPV18-positive cell lines. Furthermore, the skilled artisan cannot envision the claimed method of preventing said disease condition in animal. As indicated in preceding comments, the guidance given by the specification on how to treat or prevent the disorders or diseases is absent. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures,

diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 13-14, 20, 22-23, 31, 32, 33 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Rotstein et al. (Carcinogenesis, 1988, 9(9), 1547-51).

Rotstein teaches the use of disulfiram (a compound of formula (II)) for treating or preventing cancer by treating papillomas, which are population of putative precancerous lesions.

Although Rotstein is silent about (i) "a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene" in claim 13; "the chelated metal cation domain is a chelated zinc cation domain" in claims 31 and 40; "the chelated zinc is the sequence motif cys-X2-cys-X29-cys-X2-cys" in claim 32; and "facilitate disruption of the chelated metal cation domain and directly or indirectly determining the amount of chelated metal cation released wherein the amount of chelated metal cation released is indicative of the disruption of the chelated metal cation domain" in claim 40, such recitations of inherent properties are not limiting to the interpretation. Thus, the reference anticipates the claimed invention.

Response to Arguments

Applicant's arguments filed September 11, 2003 have been fully considered but they are not persuasive.

7. Applicant's argument takes position that the potential suitability of a compound can be determined by directly or indirectly measuring the amount of a metal cation released when the compound is contacted with a protein molecule containing a chelated metal cation domain by means of performing TSQ, BIOCORE and WSTI assays described in the specification. Applicant alleges that the determination of whether the compounds fall within the scope of claim 40 or not would be readily apparent to those skilled in the art without undue amount of experimentation. The examiner disagrees. Unlike applicant's allegation, the potentially suitable compounds interested in this invention and tested for their activity in "facilitating the disruption of chelated metal cation domain" are only limited to the compounds represented by the formula (I) or (II). Applicants fail to provide sufficient information or guidance allowing the skilled artisan to make and use the claimed full scope of "a compound capable of facilitating the disruption of a chealted metal cation domain of a protein encoded for by an MPV gene" other than the disclosed compounds represented by the formula (I) or (II). Therefore, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all potential compounds "capable of facilitating the disruption of a chelated metal cation domain" that would be enabled in this specification.

8. With respect to applicant's argument regarding "one of ordinary skill in the art would recognize that although compounds which exhibit activity in all 3 of the described assays might be preferred (see page 23, lines 21-26) other compounds of formula (I) and (II) administered as a

pharmaceutically acceptable derivative may be effective in inhibiting the growth of MPV cell lines", the examiner agrees with applicant that such could be determined by routine experimentation.

9. Applicant's argument takes position that one of ordinary skill in the art would recognize that a compound which disrupts the E6 and/or E7 zinc fingers would reasonably be expected to treat a disease or condition caused by an HPV since (i) the oncogenes E6 and E7 of HPV types are homologous and have similar functions; and (ii) the E6 and E7 proteins are essential for the formation and persistence of HPV-associated lesions and the zinc fingers of HPV E6 and/or E7 are required for their cellular function. The examiner agrees that the HPV genome contain 8 genes comprised of 6 early genes (E1, E2, E4, E5, E6 and E7) and 2 late genes (L1 and L2) and the oncogenes E6 and E7 of HPVs are homologous and have similar functions as E6 and E7 of HPV 16 and HPV 18. However, the examiner disagrees that the disruption of E6 and/or E7 zinc fingers by the compounds would provide reasonable expectation to one of ordinary skill in the art to recognize that the claimed compounds can treat all the claimed condition or disease caused by all HPVs, more broadly the claimed genus of mammalian papilloma viruses (MPV) as the claimed invention. There is no sufficient information provided in the specification that oncogenes E6 and E7 of HPVs are definite contributing factor for the entire scope of the claimed disease conditions by MPV. Furthermore, in light of the state of art at the time of the invention was made that there is no absolute correlation between the activity of HPV E6 and/or E7 proteins and the development of all of the claimed conditions caused by mammalian papilloma viruses (MPV). The specification provides insufficient written description to support the genus encompassed by the claim. Furthermore, the specification does not clearly provide an adequate

representation regarding how to prevent or cure the disease conditions. The state of the art recognizes the treatment of symptoms of the specific disorders such as cervical cancer, cervical intraepithelial neoplasia or squamous intraepithelial lesions or genital warts but not their cure. Thus, the skilled artisan cannot envision the claimed method of preventing said disease condition in animal without significant guidance from the specification or prior art to prevent or cure the diseases or conditions as required in the instant claims. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for preventing it.

10. Applicant's argument takes position that the referenced antisense ODNs (taught in Tran et al.) does not fall on the scope of the compound which facilitates the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene since the antisense ODNs involve the use of short complementary oligonucleotides to interfere with the function of mRNAs. This argument is found persuasive. Therefore, the examiner withdraws this rejection.

11. Applicant's argument takes position that Rotstein's teaching of using disulfiram (a compound of formula II) in inhibiting tumor progression by acting as antioxidants differs from those of the compounds described in the instant invention that are drawn to "facilitating the disruption of chelated metal cation domain of a protein encoded for by an MPV gene". The examiner agrees with applicant that the mechanism of action for the instant invention and that described by Rotstein are different. However, the reference directing the administration of same composition inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by Applicant anticipates Applicant's claims even absent explicit recitations of the mechanism of action. The fact that the applicant may have discovered a new pharmacological mechanism for

the claimed compound is not considered patentably distinctive over the prior art which are directed to the same therapeutic application.

Conclusion

12. Applicant's amendment necessitated a new ground of rejection in this Office action. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

VICKIE KIM
PRIMARY EXAMINER

Brian Kwon
Patent Examiner
AU 1614